REMARKS/ARGUMENTS

In this Amendment, the status of the claims is as follows: claims 1-49 and 96 have been canceled; claims 50-93 have been amended; claim 94 and claim 95 are original claims; and new claims 97-124 have been added. It is submitted that no new matter has been added by virtue of the amended and new claims, which are supported by the disclosure and claims of the application as originally filed and by the previously presented claims.

Claims 50-93 have been generally amended to reflect stylistic changes in the claim language. More specifically, claims 51 and 73, as currently amended, find support in the instant specification, *inter alia,* on page 8, last paragraph to page 9, first paragraph; on page 12, second paragraph and on page 11, Table 1, Examples (i.e., "Formulation Numbers") 6-10, which correspond to paragraph [0023], Table 1, and paragraph [0029], respectively, of Applicants' published application no. 20020106403.

New claims 97 and 98 find support in the instant specification, *inter alia,* on page 8, last paragraph to page 9, first paragraph; on page 12, second paragraph and on page 11, Table 1, Examples (i.e., "Formulation Numbers") 6-10, which correspond to paragraph [0023], Table 1, and paragraph [0029], respectively, of Applicants' published application no. 20020106403. Further support is found in the instant specification, *inter alia,* on page 10 and paragraph [0027] of Applicants' published application no. 20020106403. New claims 99-124 are supported by the prior claims and throughout the disclosure of the instant specification and published application.

Accordingly, claims 50-95 and 97-124 as currently pending in this application are presented in condition for allowance or in better form for appeal.

Applicants submit that the rejections in the 06/23/2004 Office Action have been addressed herein as if they had been asserted against the presently amended and new claims.

The claims fulfill the requirements of 35 U.S.C. § 103(a)

Claims 50-95 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over previously-cited international publication, WO 98/07414.

The Examiner alleges that WO 98/07414 "discloses the same process of preparation for the rapidly dispersing oral dosage forms of hydrophobic compounds wherein the particles are coated with at least two surfactants; one of the surfactants is a phospholipid (surface acting agent)". The Examiner further contends that "[t]he process by WO differs from the claimed process ... in that, the bulking agent is added along with the active agent and the surface modifiers" and cites to the paragraph bridging pages 7 and 8 of WO 98/07414 as teaching "mannitol and other agents may be added to adjust the final formulation to isotonicity as well as a stabilizing agent during drying". According to the Examiner, from this teaching it would have been obvious to one of ordinary skill in the art that the addition of mannitol is a manipulatable parameter, which can be added either before or after the homogenization step with the expectation of obtaining the best possible stabilized product.

Applicants respectfully disagree that WO 98/07414 discloses the "same process" of preparing rapidly dispersable oral dosage forms of a water-insoluble or poorly water-soluble drug, as is presently claimed by Applicants. Indeed, WO 98/07414 does not disclose Applicants' presently claimed process, and all elements thereof, considered in its entirety. Applicants further submit that the WO 98/07414 disclosure contains no teaching or suggestion that would lead one skilled in the art to reasonably expect that a dried, e.g., freeze-dried, suspension prepared according to Applicants' presently claimed invention can be stored at high temperature and humidity without a loss of the redispersibility characteristic of the reconstituted particles. Applicants' process surprisingly provides dried particles that are essentially devoid of particle aggregation, even after reconstitution following periods of storage. *See,* e.g., the instant specification on page 8, last paragraph to page 9, first paragraph; page 12, second paragraph and page 11, Table 1, Examples (i.e., "Formulation Numbers") 6-10, which correspond to paragraph [0023], Table 1, and paragraph [0029], respectively, of Applicants' published application no. 20020106403.

It is submitted that the presently claimed invention must be considered as a whole in determining differences between the prior art and the presently claimed invention. M.P.E.P. §2141.02. Considered in its entirety, the presently claimed invention provides a process of producing better dispersibility of micronized particles by virtue of the performance of the steps

comprising the process. Further, all claim limitations must be taught or suggested by the cited art reference. M.P.E.P. §2143.03. In the instant case, WO 98/07414 is silent regarding the entirety of the steps of a method that would lead one having skill in the art to achieve Applicants' presently-claimed, multi-step method of preparing rapidly disintegrating solid particles comprising drug. Moreover, WO 98/07414 does not perform the steps of Applicants' process considered as a whole, and does not recognize or obtain Applicants' results. Consequently, the present invention, considered as a whole, provides an advancement in the art, which is not remotely taught or suggested by the WO 98/07414 publication, considered in its entirety.

WO 98/07414 is directed to the preparation of surface stabilized drug microparticles that maintain their size over time, due to a retardation of drug particle growth during prolonged storage. (*See,* WO 98/07414 at page 3, lines 10-12; page 4, lines 1-3; page 7, lines 4-8; and Examples 1 and 4-6). This international publication does not teach or suggest the multi-step process as presently claimed by Applicants. Indeed, the process described by WO 98/07414 merely involves mixing particles of a compound of interest with a phospholipid and at least one surfactant and applying energy to the mixture to produce volume-weighted mean particle size values of the compound that are at least 50% smaller than the size values of particles produced in the absence of surfactant.

Applicants' distinct process involves steps leading to the preparation of drug-containing particles dispersed and embedded throughout a support matrix that dissolves or substantially disperses in a rapid disintegration time upon contact between the solid and an aqueous environment, resulting in a release of the surface stabilized drug particles into the aqueous environment as a suspension; and wherein, after contact between the solid and the aqueous environment, the resulting suspension comprises no more than 20% by weight of aggregated or agglomerated primary particles.

WO 98/07414 is not concerned with rapid particle dispersibility within a support matrix. WO 98/07414 does not teach or disclose the steps and elements that comprise Applicants' presently claimed process leading to a rapidly disintegrating solid dosage form of a water insoluble or poorly water soluble drug. The general disclosure in WO 98/07414 that mannitol

may be added to adjust the final formulation to isotonicity, or as a stabilizing aid, does not make obvious an entire process comprising the discrete steps and admixed ingredients that were discovered by the Applicants to provide rapidly releasable drug from solid particles after encountering an aqueous environment. As a result of the practice of Applicants' process, upon contact of the solid particles and with the aqueous environment, the resulting suspension comprises no more than 20% by weight of aggregated or agglomerated primary particles. Such a process, and the results thereof, are not remotely recognized or suggested by the disclosure of WO 98/07414.

In Applicants' presently claimed, multi-step process, a water insoluble or poorly water soluble drug is first mixed with surface stabilizing agents, one of which must be a phospholipid, to form an aqueous suspension that is subjected to particle fragmentation to form a homogeneous aqueous suspension. Thereafter, or prior to drying, the homogeneous suspension is mixed with one or more bulking/releasing agents, or a combination thereof, to form a solid matrix. Following this step, the homogeneous suspension, admixed with the one or more matrix forming bulking/releasing agents, is dried to form a solid in which surface stabilized drug is dispersed and embedded throughout the support matrix.

WO 98/07414 does not teach that combinations of surface acting agents, one of which is a phospholipid, in conjunction with one or more bulking/releasing agents, in a process of forming readily disintegratable particles, will produce particles dispersed and embedded throughout a support matrix, which particles have essentially the same particle sizes both before drying, e.g., by lyophilization, and after drying upon reconstitution. *See,* for example, the instant specification on page 8, last paragraph to page 9, first paragraph; on page 12, second paragraph and on page 11, Table 1, Examples (i.e., "Formulation Numbers") 6-10, which correspond to paragraph [0023], Table 1, and paragraph [0029], respectively, of Applicants' published application no. 20020106403.

WO 98/07414 simply does not teach all of the elements of Applicants' claimed process and does not recognize or contemplate a process that yields rapidly dispersing microparticles having the properties that are described and claimed in the instant application. The process of stabilizing drug-containing particles as described in WO 98/07414 is distinct from Applicants'

process as presently claimed. In Applicants' process, surface acting agents, one of which is a phospholipid, are combined with drug to form a drug/phospholipid suspension that is fragmented to form a homogeneous suspension and admixed with one or more matrix-forming bulking/releasing agents prior to drying to form drug-containing particles that rapidly disperse, dissolve and release their drug component in an aqueous environment.

Moreover, the practice of Applicants' presently claimed process does not cause irreversible particle aggregation and/or particle agglomeration and without particle size growth. Surprisingly, Applicants' process leads to dried particles which, upon reconstitution, have essentially the same degree of dispersity as does the pre-dried suspension, with the suspension comprising no more than 20% by weight of aggregated primary particles after contact between the solid particles and aqueous environment. Only the Applicants teach this process and provide an advancement to the art by virtue of their inventive discovery.

Without the very disclosure and teaching that is provided by the Applicants, there is no teaching or suggestion provided by WO 98/07414, considered in its entirety, that would lead one having skill in the pertinent art to make the modifications necessary, i.e., to add or use additional steps and elements, to arrive at Applicants' invention as presently claimed.

In view of the foregoing, it is submitted that the present invention is patentably distinct from and unobvious over the WO 98/07414 publication. Applicants therefore respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

Claims 50-95 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Yarwood (U.S. Patent No. 5,827,541), (hereinafter "Yarwood"), by itself, or further in combination with Green (U.S. Patent No. 5,976,577, of record), (hereinafter "Green"), or Na (U.S. Patent No. 5,326,552), (hereinafter "Na"), or WO 98/07414, by themselves or in combination.

According to the Examiner, Yarwood discloses "a process for the rapidly dispersing oral dosage forms of hydrophobic compounds wherein the particles are coated with a surfactant

(surface modifying agent)", namely poloxamer. However, Yarwood does not disclose phospholipids as the surfactant and does not teach a combination of surfactants. The Examiner opines that, based on Yarwood's general statement and suggestion that "any surfactant which fulfills the requirement of pharmaceutical acceptability may be used in the invention", it would be obvious to one of ordinary skill in the art to use phospholipids in the process of Yarwood with a reasonable expectation of success.

It is submitted that Yarwood alone, or in combination with the other cited references discussed below, does not make obvious Applicants' presently claimed invention. Yarwood does not teach or suggest all of Applicants' claim limitations, as is required pursuant to M.P.E.P. §2143.03. In the instant case, Applicants' presently claimed process and the process described by Yarwood reflect distinct and different methods of preparing rapidly disintegrating dosage forms of a hydrophobic active substance. Yarwood's contemplated process of preparing oral dosage forms involves the admixture of an active substance in a solvent containing a pharmaceutically acceptable surfactant and a carrier material to form a homogeneous suspension. This suspension is then dispensed by aliquot into discrete units, and frozen or gelled prior to drying to produce the final dosage form.

As can be seen from Applicants' Examples in Table 1 on page 11 of the specification as filed, Applicants' claimed process comprising admixture of drug, surfactant, phospholipid and bulking/releasing agent, in combination, provides the ability of the dried particles formed by the method not to irreversibly aggregrate and to have essentially the same dispersibility both pre- and post-lyophilization. (*See,* for example, page 13, first full paragraph of the as-filed specification, and paragraph [0032] of Applicants' published patent application no. 20020106403). In addition, the particles prepared according to the presently claimed process allow recovery of the original suspension particle following drying, e.g., by lyophilization. *See,* for example, page 12, first paragraph of the as-filed specification, and paragraph [0028] of published patent application no. 20020106403. These features of the presently claimed invention are neither taught nor suggested by Yarwood and the cited art, either alone or in combination.

Importantly, Yarwood's sole Example (Col. 5, lines 1-24) does not include a phospholipid in combination with an active agent, one or more surface stabilizing agents and one or more bulking/releasing agents. Thus, Yarwood's example is akin to Examples/Formulations 3-5 presented in Table 1 on page 11 of Applicants' original specification. Examples/Formulations 3-5 in Applicants' Table 1 demonstrate that, without the appropriate combination of elements in the process taught by Applicants, the resulting particles possess inferior attributes of disintegration time and particle size when assessed both in pre-dried and post-dried form, i.e., following reconstitution. Thus, Yarwood's method is not only distinct from, but is plainly inferior to, Applicants' presently claimed process.

Yarwood does not teach or contemplate the steps of a method that would lead one having skill in the art to achieve Applicants' presently-claimed, multi-step method of preparing rapidly disintegrating solid particles comprising drug. The present invention, which must be considered as a whole, provides a process that is distinct from the teachings of Yarwood, considered in its entirety.

In fact, Yarwood distinguishes itself from disclosures and preparations involving the use of matrix forming components, which, according to Yarwood, can result in a lack of uniformity of content of drug in the final product. Yarwood characterizes such preparations as presenting problems in the art which the method of Yarwood is said to overcome. (*See,* Yarwood at Col. 1, lines 43-56). Unlike Applicants' process, Yarwood's method involves a carrier material, such as gelatin, to form a network that carries a dosage of the active substance. (*See,* Yarwood at Col. 1, lines 60-67 and at Col. 3, lines 65-67 bridging Col. 4, lines 1-14). Thus, Yarwood teaches away from Applicants' presently claimed invention, which involves the use of matrix-forming bulking/releasing agents, and combinations thereof, admixed with phospholipid-coated, drug-containing particles. Such a teaching away from Applicants' presently claimed invention is indicative of the non-obviousness of the presently claimed invention in view of Yarwood.

The combination of surface stabilizing agents, phospholipid and bulking or releasing agents admixed with drug in accordance with the steps of Applicants' inventive process is specifically lacking in Yarwood's method. Thus, Yarwood provides a patentably distinct procedure for obtaining dissolvable drug-containing particles. The disclosure of Yarwood does

not suggest or contemplate the specific use of phospholipid in combination with other elements employed in Applicants' process and therefore does not make obvious Applicants' newly described process, which allows the recovery of a non-aggregated particulate suspension following reconstitution of the dried dosage form. Thus, Applicants' presently claimed process provides advantageous and surprising properties as described in the instant application. (*See,* e.g., the instant specification on page 8, last paragraph to page 9, first paragraph; on page 12, second paragraph and on page 11, Table 1, Examples (i.e., "Formulation Numbers") 6-10, which correspond to paragraph [0023], Table 1, and paragraph [0029], respectively, of Applicants' published application no. 20020106403).

Without Applicants' teaching, there is no motivation to manipulate the basic method of Yarwood with an expectation of the best possible results, contrary to the Examiner's statement on page 4 of the 06/23/2004 Office Action. Applicants' comparative results demonstrate that Applicants' process, considered as a whole, including all of its elements, is unobvious in view of the teaching of Yarwood.

Applicants respectfully contend that Yarwood's general statement that "any pharmaceutically acceptable surfactant can be used" is to be understood in the light of Yarwood's own method as described and contemplated by Yarwood. Yarwood is silent concerning the use of one or more surface stabilizing agents, of which at least one must be a phospholipid, along with matrix-forming bulking/releasing agents, as is required in the presently claimed invention. In contrast to Applicants' invention as presently claimed, Yarwood also does not recognize, contemplate, or teach that dried particles prepared by Yarwood's method are essentially the same following reconstitution as the original particle suspension. It is the combination of Applicants' elements comprising the steps of Applicants' claimed process that provide to the art rapidly dispersible, non-irreversibly-agglomerating particles having the properties discovered and taught by Applicants.

Turning to Green, the Green patent, alone or in combination with Yarwood, does not compensate for the deficiencies of Yarwood, the primary reference. Thus, these references do not lead one having ordinary skill in the art to make the modifications necessary to arrive at Applicants' presently claimed invention with a reasonable expectation of success. Green

teaches that phospholipids are among many types of polymer or lipid materials that may be used to coat particles. However, Green does not teach Applicants' presently claimed process, nor does Green contain all elements of Applicants' process.

Indeed, Green teaches away from the presently claimed invention because Green employs, and strives to attain, larger sized particles. Specifically, according to Green, "the larger sized particles employed allows for the formation of a continuous intact coating on the drug particles which prevents or minimizes early release of the drug during processing ...". (*See,* Green at Col. 5, lines 9-14). Green's optimum coated particle size is disclosed to be in the region of about 50 μm to 400 μm, preferably about 100-300 μm (Col. 5, lines 6-8 of Green). Clearly, particles of the size taught and contemplated by Green are outside of the scope of Applicants' presently claimed invention.

In addition, Applicants have earlier provided clear evidence showing that the teachings of Green result in agglomerated and not fully dissociated particles which, upon rehydration, do not give a suspension that is similar to the suspension before drying, e.g., by lyophilization. *See,* Declaration under 37 C.F.R. §132 of Awadhesh Mishra, of record. Thus, Green, alone or in combination with the other cited references, teaches a distinct process that does not negate the patentability of Applicants' presently claimed process, considered as a whole.

In view of the distinctions between the teachings and disclosure of Yarwood and the presently claimed invention, as discussed at length hereinabove, it is submitted that one skilled in the art would not be led to combine Yarwood and Green so as to arrive at Applicants' invention as presently claimed with a reasonable expectation of success. Yarwood in combination with Green would not result in the presently claimed invention, especially since both of these references lack, and do not recognize or compensate for, the very teachings and advances that Applicants provide to the art.

Concerning Na, the Na patent does no more than Green to make up for the deficiencies of Yarwood as primary reference. Na contains disclosure that would not allow one having skill in the art to achieve Applicants' presently claimed invention, were one to combine the teachings of Na with the other cited references. Na discloses an X-ray contrast composition comprising

particles of an organic diagnostic X-ray contrast agent. The particles have adsorbed on their surfaces a high molecular weight surface modifier and a cloud point modifier so as to maintain an effective average particle size of less than 400 nm. (Col. 3, lines 25-39 of Na).

Na does not teach or contemplate Applicants' presently claimed processes to produce a solid in which surface stabilized drug particles are dispersed and embedded throughout a support matrix formed by one or more matrix-forming agents, wherein the particles have a mean volume weighted particle size ranging between about 0.05 and about 10 micrometers. Na et al. teaches and contemplates nanoparticles containing X-ray diagnostic compounds that are clearly smaller than the drug-containing solid particles produced by Applicants' presently claimed processes. Following the teaching of Na, there is no reasonable expectation of success in attaining particles having the attributes of those described by Applicants, in view of Na's distinct method and the size difference between Na's particles containing X-ray contrast agent and those prepared by the practice of Applicants' presently claimed invention.

Applicants' claimed method, considered as a whole, is not made obvious by Na, taken alone or in combination with Yarwood, Green and WO 98/07414. Na does not remotely recognize or appreciate Applicants' process that results in a solid having surface stabilized drug particles dispersed and embedded throughout a support matrix formed by the one or more matrix-forming bulking/releasing agents, or a combination thereof. In Applicants' process, unlike the methods described in Na and the other cited references, the support matrix dissolves or substantially disperses in a rapid disintegration time upon contact between the solid and aqueous environment. This results in a release of the surface stabilized drug particles into the aqueous environment as a suspension essentially without irreversible particle aggregation and/or particle agglomeration and without particle size growth, wherein the resulting suspension comprises no more than 20% by weight of aggregated or agglomerated primary particles.

With specific regard to WO 98/07414, the distinctions between this cited reference and the presently claimed invention have been set forth at length above and apply equally in the present rejection under §103. Accordingly, for the reasons discussed herein, WO 98/07414, alone or in combination with Yarwood, Green and Na, does not make obvious Applicants' invention as presently claimed.

In view of the foregoing, it is submitted that the presently claimed invention is patentably distinct from and unobvious over the cited references of Yarwood, Green, Na and WO 98/07414, taken alone or in combination. Applicants therefore respectfully request withdrawal of this rejection under 35 U.S.C. §103(a).

CONCLUSION

Applicants respectfully submit that the present application is now in condition for allowance. An action progressing this application to issue is courteously urged.

Should any additional fees be deemed to be properly assessable in this application for the timely consideration of this Amendment, or during the pendancy of this application, the Commissioner is hereby authorized to charge any such additional fee(s), or to credit any overpayment, to Deposit Account No. **50-0311**; Reference No. **28069-546**; Customer No. **35437**.

Should any extension of time be required for the timely consideration of this Amendment and response, the Commissioner is hereby authorized to grant any such extension of time as may be necessary, and to charge any additional fee(s) owed by Applicants for such extension of time, to the above-mentioned Deposit Account, Reference and Customer Numbers.

If the Examiner believes that further discussion of the application would be helpful, he is respectfully requested to telephone Applicants' undersigned representative at (212) 692-6742 and is assured of full cooperation in an effort to advance the prosecution of the instant application and claims to allowance.

Respectfully submitted,

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